Impact of gut-derived metabollites on substrate metabolism and metabolic health

Valorization

This thesis describes the potential of gut-derived microbial metabolites as key players in host metabolic health and insulin sensitivity. We investigated the role of short chain fatty acids and branched chain fatty acids (SCFA and BCFA) in *in vivo* metabolic health in human cross-sectional and intervention studies with overweight people and with obesity. In addition, we studied the role of SCFA in human derived adipose and skeletal muscle tissues in *in vitro* models. In this section, we describe the impact of our scientific findings for global society and economy, especially on the implications and possible applications for specific target groups with higher health risks.

Obesity is associated with other comorbidities including cardiovascular disease, type 2 diabetes mellitus, some forms of cancer among other comorbidities [1]. Currently, obesity prevalence and related complications are continuing to increase as reported by the World Health Organization with prevalence rates of obesity of 2 billion according to 2016 report [1]. Most affected areas include parts of Europe, North America (i.e. Mexico) and the Middle East [1]. Of major importance, predictions point towards even higher increments in the near future.

Obesity is a chronic metabolic disease that results from an energy imbalance in the long-term. The major contributing factors to complications include an increased lipid accumulation in adipose and non-adipose organs, adipose tissue dysfunction, lipid spillover and low-grade inflammation that collectively result in the development of insulin resistance. These metabolic alterations may start with a mild insulin resistant state and progress to type 2 diabetes mellitus.

In the last decades, research has shown the intricate connection of the gut and gut microbial-derived metabolites with host metabolic health. In this context, this thesis provides valuable information about major saccharolytic fermentation products (acetate, propionate and butyrate) and less abundant gut-derived metabolites (lactate, caproate, valerate, succinate) as well as proteolytic fermentation products (isovalerate and isobutyrate). This sheds light on the individual as well as collective effects of these metabolites on host metabolic health and insulin sensitivity.

For instance, we discuss the possible higher relevance of circulating SCFA as compared to fecal concentrations as biomarkers of metabolic health effects. Although this particular finding warrants further investigation, this may be of importance in the clinical setting and monitoring of nutritional interventions targeting the gut. Furthermore, we show that the relationship of the major SCFA acetate with insulin sensitivity together with the sexual dimorphism in this

relationship is complex and warrants further investigation. Of note, these findings point towards the need for carefully designed studies to investigate SCFA (i.e. acetate) kinetics (production, absorption and release into the circulation) in relation to metabolic health.

In general, this thesis adds to the knowledge on the potential of gut-derived metabolites to modulate host metabolic health, especially in the human situation. In this regard, our findings may provide useful information for dietary intervention strategies that may ameliorate metabolic health. It is evident that attention should be placed on the balance between saccharolytic and proteolytic fermentation as a determinant of metabolic health. Furthermore, our data may provide clues for a more targeted dietary guidance based on microbial and metabolic phenotype. After further confirmation of these findings in prospective dietary intervention studies, this knowledge may be used by health care professionals when advising patients on their dietary intake as well as relevant leads for food industry to produce functional foods with pronounced metabolic benefits.

Of note, the *in vitro* studies of this doctoral thesis provided valuable scientific input on tissue-specific effects of SCFA. These studies provided important mechanistic insight on previous described metabolic effect on lipolysis and fat oxidation after colonic SCFA administration *in vivo*. However, more research is needed to define effective dietary interventions (pre, pro, synbiotics) that can increase systemic SCFA levels in physiologically relevant concentrations, thereby eliciting similar effects, as reported in vitro, at the tissue level in skeletal muscle and adipose tissue or other tissues.

This thesis was partly funded by a Kootstra Talent grant from Maastricht University Medical Centre+ obtained by Emanuel Canfora. In addition, this thesis was possible through a Scholarship granted to Manuel Gonzalez by Consejo Nacional de Ciencia y Tecnologia (CONACYT), a public agency of Mexico's federal government. In this thesis, we used large dataset including data from the large European project DiOGenes. In this context, this thesis contributes to a broader and cross atlantic/global perspective that stimulated collaboration and benefited all parties in gaining knowledge concerning obesity.

All the work in this thesis will be available to the public through scientific publications in internationally peer-reviewed journals. In addition, there has been frequent interaction in research meetings, symposiums (School of Nutrition and Translational Research in Metabolism, NUTRIM) and conferences at the national (Netherlands Association for the Study of Obesity, NASO Utrecht 2018 and 2019) and international level (European Congress of Obesity, ECO Vienna 2018 and Glasgow 2019).

The overall aim of the thesis was to gain more insight into gut microbial metabolites and their impact on metabolic health by utilizing state of the art methodology and extensive human phenotyping. In addition, we used human derived skeletal muscle and adipose tissue *in vitro* models, which provided valuable insight into human physiology that was previously lacking.

Previous work has focused on identifying nutritional interventions (i.e. prebiotics) and their capacity to produce microbial metabolites that can improve metabolic health. Accumulating evidence suggests that the obesity pandemic may increase susceptibility and worsen the current coronavirus disease 2019 (COVID-19) outcomes possibly partially linked to alterations in microbial community [2, 3]. However, future research has to elucidate whether nutritional interventions promoting anti-inflammatory properties, gut and metabolic health may ameliorate COVID-19 infections and the progression of the disease [4].

To conclude, this thesis provides input on the role of saccharolytic (SCFA) and proteolytic fermentation products (BCFA) in metabolic health in human studies and human derived cell models. Of note, this may lead to design more carefully and personalized human interventions and investigate in more detail the role of microbial metabolites in metabolic health in response to nutritional interventions. Finally, this may aid in the development of more personalized nutritional strategies that counteract the impact of obesity and its comorbidities more effectively than or in addition to conventional caloric restriction.

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